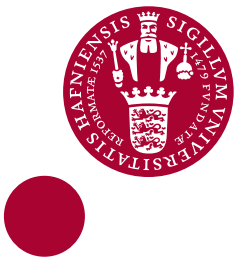

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Published in:
World Journal of Transplantation

DOI:
10.5500/wjt.v8.i5.188

Publication date:
2018

Document version
Publisher's PDF, also known as Version of record

ISSN 2220-3230 (online)

World Journal of *Transplantation*

World J Transplant 2018 September 10; 8(5): 122-197

Published by Baishideng Publishing Group Inc

World Journal of Transplantation

Contents

Volume 8 Number 5 September 10, 2018

ABOUT COVER

Editorial Board Member of *World Journal of Transplantation*, Felix Cantarovich, MD, Professor, Clinical renal transplantation, Catholic University Argentine, 9 rue Parent de Rosan, Paris 75016, France

AIM AND SCOPE

World Journal of Transplantation (*World J Transplant*, *WJT*, online ISSN 2220-3230, DOI: 10.5500) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

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AIM AND SCOPE

World Journal of Transplantation (*WJT*) is now abstracted and indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), and Superstar Journals Database.

NAME OF JOURNAL
World Journal of Transplantation

ISSN
ISSN 2220-3230 (online)

LAUNCH DATE
December 24, 2011

EDITORIAL OFFICE
Jin-Lei Wang, Director
World Journal of Transplantation
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA

Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
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PUBLISHER
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLICATION DATE
September 10, 2018

World Journal of Transplantation

Submit a Manuscript: http://www.f6publishing.com

World J Transplant 2018 September 10; 8(5): 188-197

DOI: 10.5500/wjt.v8.i5.188

ISSN 2220-3230 (online)

ORIGINAL ARTICLE

Randomized Clinical Trial

Clinical features and determinants of VO_{2peak} in *de novo* heart transplant recipients

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Author contributions: Rolid K coordinated the study, collected and analyzed the data and drafted the paper; Andreassen AK contributed to the inclusion of the participants in Norway and in further drafting of the paper; Yardley M and Bjørkelund E contributed to data collection in Norway; Karason K was responsible for the study in Sweden; Wigh JP was responsible for coordination and data collection in Sweden; Dall CH coordinated and collected data in Denmark; Gustafsson F was responsible for the study in Denmark; Gullestad L and Nytrøen K designed the research, were project leaders and participated in further drafting and analyses of the data; all authors contributed to critical revision and editing and approval of the final version.

Supported by the Norwegian Health Association, No. 12906; Scandiatransplant; and the South-Eastern Norway Regional Authority, No. 2013111.

Institutional review board statement: The study was approved by the South-East Regional Committee for medical and health research ethics in Norway and the Committee for medical and health research ethics in Sweden and Denmark.

Clinical trial registration statement: This study is registered at ClinicalTrials.gov. The registration identification number is NCT01796379.

Informed consent statement: All study participants gave their written consent prior to study inclusion.

Conflict-of-interest statement: None of the authors have any conflict of interest to declare.

CONSORT 2010 statement: We have prepared the manuscript according to the CONSORT 2010 statement, where appropriate. A pdf version of the document is uploaded.

Manuscript source: Unsolicited manuscript

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Received: June 23, 2018
Peer-review started: June 24, 2018
First decision: July 19, 2018
Revised: July 29, 2018
Accepted: August 6, 2018
Article in press: August 6, 2018
Published online: September 10, 2018

Abstract

AIM

To study exercise capacity and determinants of early peak oxygen consumption (VO_{2peak}) in a cohort of *de novo* heart transplant (HTx) recipients.

METHODS

To determine possible central (chronotropic responses, cardiopulmonary and hemodynamic function) and peripheral factors (muscular exercise capacity and body composition) predictive of VO_{2peak}, a number of different measurements and tests were performed, as follows: Cardiopulmonary exercise testing (CPET) was performed mean 11 wk after surgery in 81 HTx recipients > 18 years and was measured with breath by breath gas exchange on a treadmill or bicycle ergometer. Metabolic/respiratory measures include VO_{2peak} and VE/VCO_2 slope. Additional measures included muscle strength testing, bioelectrical impedance analysis, echocardiography, blood sampling and health-related quality of life. Based on the VO_{2peak} (mL/kg per minute) median value, the study population was divided into two groups defined as a low-capacity group and a high-capacity group. Potential predictors were analyzed using multiple regression analysis with VO_{2peak} (L/min) as the dependent variable.

RESULTS

The mean ± standard deviation (SD) age of the total study population was 49 ± 13 years, and 73% were men. This *de novo* HTx cohort demonstrated a median VO_{2peak} level of 19.4 mL/kg per min at 11 ± 1.8 wk post-HTx. As compared with the high-capacity group, the low-capacity group exercised for a shorter time, had lower maximal ventilation, O_2 pulse, peak heart rate and heart rate reserve, while the VE/VCO_2 slope was higher. The low-capacity group had less muscle strength and muscular exercise capacity in comparison with the high-capacity group. In order of importance, O_2 pulse, heart rate reserve, muscular exercise capacity, body mass index, gender and age accounted for 84% of the variance in VO_{2peak} (L/min). There were no minor or major serious adverse events during the CPET.

CONCLUSION

Although there is great individual variance among *de novo* HTx recipients, early VO_{2peak} measures appear to be influenced by both central and peripheral factors.

Key words: Cardiopulmonary exercise testing; Early VO_{2peak}; *De novo* heart transplant; Health related quality of life; Muscle strength

Core tip: This *de novo* heart transplant (HTx) cohort demonstrated a median peak oxygen consumption (VO_{2peak}) level of 19.4 mL/kg per min at 11 ± 1.8 wk post-HTx, which is comparable to what is shown in maintenance HTx recipients. VO_{2peak} in this study was determined by both central and peripheral factors. The strongest predictors were O_2 pulse, heart rate reserve and muscular exercise capacity. Maximal exercise testing provides valuable information for clinical use and future prognosis and can be safely performed as early as 11 wk post-HTx.

Rolid K, Andreassen AK, Yardley M, Bjørkelund E, Karason K, Wigh JP, Dall CH, Gustafsson F, Gullestad L, Nytrøen K. Clinical features and determinants of VO_{2peak} in *de novo* heart transplant recipients. *World J Transplant* 2018; 8(5): 188-197 Available from: URL: http://www.wjgnet.com/2220-3230/full/v8/i5/188.htm DOI: http://dx.doi.org/10.5500/wjt.v8.i5.188

INTRODUCTION

Cardiac rehabilitation, including exercise training to improve exercise capacity and health-related quality of life (HRQoL) is recommended after heart transplant (HTx)[1], but there are no clear and specific guidelines for how, how often or at what intensity exercise training should be performed.

Exercise capacity is often severely reduced shortly after HTx with peak oxygen consumption (VO_{2peak}) levels reported to be between 9.2 and 19.7 mL/kg per min[2-12]. However, early measurement of VO_{2peak} is not routine in most centers. VO_{2peak} is the gold standard to objectively assess functional limitation and give an assessment of the integrative physiology involving cardiovascular, pulmonary, muscular, cellular and oxidative systems[13,14]. It has also been reported that VO_{2peak} is a strong predictor for survival in HTx recipients[15,16]. In studies of maintenance HTx patients, VO_{2peak} seems to be determined by both central (chronotropic incompetence, reduced stroke volume and cardiac output, impaired systolic and diastolic function, pulmonary dysfunction) and peripheral factors (diminished skeletal muscular capacity)[1,17-19]. Other factors, like donor characteristics, diagnosis and deconditioning before transplantation may also be associated with reduced exercise capacity after HTx[18]. However, we have recently reported that the most important variables predicting VO_{2peak} in maintenance HTx patients are mostly of peripheral origin[20,21]. In *de novo* HTx patients, only two studies exist (n = 43[6] and n = 24[12]), which report limiting factors for VO_{2peak}. These studies indicate that both central and peripheral

factors could be involved in the early phase, but the knowledge is scarce and thus, a better understanding of factors that are associated with peak exercise shortly after HTx could guide clinicians and physiotherapist for more individualized therapy and specific exercise recommendations.

We hypothesized that both central and peripheral factors are associated with reduced exercise capacity in *de novo* HTx recipients. In the present study, we performed cardiopulmonary exercise testing (CPET) in a cohort of *de novo* HTx patients with the aim to determine clinical, hemodynamic and peripheral factors that contribute to the reduced exercise capacity.

MATERIALS AND METHODS

Patients and settings

This study was conducted in three centers in Scandinavia (Oslo, Gothenburg and Copenhagen). Altogether, 155 *de novo* HTx patients were assessed for eligibility. Of these, 72 were excluded for various reasons: did not meet inclusion criteria (cognitive issues, physical disabilities, medical complications, language barriers, contagion, no physical therapist available) (n = 43); were not motivated (n = 15); logistic reasons (n = 14). In addition, two were excluded after they had given their consent, one due to medical complications and one withdrawal. A total of 81 patients underwent CPET. The study was approved by the South-East Regional Committee for medical and health research ethics in Norway and the Committee for medical and health research ethics in Sweden and Denmark. The study was conducted in accordance with the recommendations in the Helsinki Declaration.

The current study is based on the baseline data from an ongoing randomized controlled trial (RCT): The High-intensity Interval Training in de novo heart Transplant recipients in Scandinavia (HITTS) study. The design and rationale of this study is described elsewhere[22]. In short, the RCT compares the effect of a 9-mo long two-armed intervention: High-intensity interval training versus moderate intensity continuous training.

Inclusion criteria

The inclusion criteria were: Clinically stable HTx recipients approximately 8-12 wk after HTx; Age > 18 years; Both sexes; Receiving immunosuppressive therapy according to local protocols; Patient willing and able to give written informed consent for study participation, and motivated to participate in the study for nine months.

Measurements

The primary endpoint, VO_{2peak}, was measured on a treadmill or a bicycle ergometer applying an individualized protocol with an incremental workload until exhaustion[23]. The Norwegian populations were tested on a treadmill, except for four subjects, who could not comply and were tested on a bicycle ergometer. All patients in Sweden and Denmark were tested on a bicycle, which is the customary form for exercise testing in these countries. The variables from the CPET have been described previously[22]. Common heart rate (HR) variables and abbreviations used in this study were: Peak heart rate (HR_{peak}); Percentage of age-predicted maximum HR (% HR_{max}) = [(HR_{peak}/220 - age) × 100]; Chronotropic response index (CRI) = (HR_{peak} -HR_{rest})/(220 - age/HR_{rest}); Heart rate reserve ($HR_{reserve}$) = HR_{peak} - HR_{rest}; $HR_{recovery}$ (difference between HR_{peak} and HR after 30 s, 1, 2, 3 and 4 min).

Secondary endpoints

Potential variables influencing VO_{2peak}, such as lung function, maximum muscle strength and muscular exercise capacity, bioelectrical impedance analysis, echocardiography, blood samples and HRQoL were measured.

Lung function

Different lung function variables were measured in relation to the CPET, both at rest and during exercise. Spirometry was performed at rest before CPET: Peak expiratory flow (PEF), forced expiratory volume at 1 min (FEV1), forced vital capacity (FVC) during exercise, maximum ventilation (Vmax) and ventilatory efficiency (VE/VCO_2)[14] were calculated.

Muscle strength and muscular exercise capacity

Muscle strength and muscular exercise capacity in the quadriceps and hamstring muscle groups were measured isokinetically. Five repetitions at an angular velocity of 60°/s were performed when measuring muscle maximal strength. For the muscular exercise capacity, 30 isokinetic contractions at 240°/s were performed. In the analyses, we used the bilateral sum of m. quadriceps and m. hamstrings[20,22].

Bioelectrical impedance analysis

Bioelectrical impedance is a simple and fairly valid method to measure body composition[24]. In this study, the Tanita (Tanita, Arlington Heights, IL, United States) system was used to measure body fat, body water, muscle mass, bone mass, visceral fat, metabolic age and basal metabolic rate.

Echocardiography

Standard Doppler-echocardiography was performed by experienced technicians and assessed by cardiologists to determine myocardial size and function.

Biochemistry

All patients underwent blood sampling in the morning in a fasting state. Two EDTA tubes were collected, inverted ten times and immediately placed on ice. Samples were centrifuged within 20 min. Plasma was transferred into four vials and frozen at -80 ℃. One serum tube was collected and placed in room temperature for 60 to 120 min for coagulation before centrifugation. The sample was then transferred into two vials and frozen at -80 ℃.

Plasma concentrations of N-terminal pro brain natriuretic peptide (NT-proBNP) was determined using an electrochemiluminescence immunoassay on a Modular platform (Roche Diagnostica, Basel, Switzerland), high sensitive C-reactive protein (hs-CRP) levels using a particle-enhanced, high-sensitive immunoturbidimetric assay (hsCRP, Tina-Quant CRP Gen.3), and high-sensitive troponin T (hs-TnT) was measured by electrochemiluminescence immunoassay (hsTnT, Elecsys Troponin T high sensitive, Roche Diagnostics).

HRQoL and symptoms of anxiety and depression

HRQoL was measured with the generic questionnaire short form-36, version 2 (SF-36v2)[25]. The results were transformed into norm-based scores on a standardized scale with a mean of 50 and a standard deviation (SD) of 10[25]. Subscales were aggregated into two sum-scores; physical component summary (PCS) and mental component summary (MCS). Symptoms of anxiety and depression were measured with the Hospital Anxiety and Depression Scale (HADS)[26]. The values were dichotomized using a cut-off score $\geqslant$ 8, which was considered to represent symptoms of depression or anxiety.

Statistical analysis

All data were analyzed using IBM SPSS, version 23 and version 25.0 (IBM corporation, United States). Continuous data are expressed as mean ± SD or median first quartile (Q1), third quartile (Q3), and categorical data are presented as percentages. Patients were divided by the median VO_{2peak} (mL/kg per min) value into a low-capacity group ($\leqslant$ 19.4) and a high-capacity group (> 19.4). Between-group comparisons were performed using two independent samples t or Mann Whitney *U* test. χ^2 or *F* were used for categorical data, where appropriate. Bivariate relationships were explored and univariate regression analyses were performed with potential predictors (Tables 1 and 2). To identify the degree of association with VO_{2peak}, all relevant variables with $P < 0.05$ and other potential variables from the univariate analyses of linear regression were selected for further multiple regression analyses. VO_{2peak} (L/min), adjusted for age, sex and BMI, was used as the dependent variable. The final model was built using a series of multiple regression analyses with the enter method (Table 3). Assumptions were checked for normality and linearity.

RESULTS

Clinical characteristics

The mean ± SD age of the total study population was 49 ± 13 years, and 73% were men. Patients were on average 11.1 ± 1.8 wk after HTx. The mean VO_{2peak} was 20.4 mL/kg per min, which is 56% of expected compared to the reference values described in the 9th edition of the American College of Sports Medicine's (ACSM) guidelines for exercise testing and exercise prescription[27]. Further demographic and clinical characteristics are presented group-wise in Tables 1 and 2.

Compared to the high-capacity group, the low-capacity group was characterized by a higher body mass index (BMI) and a higher fat content, they were more often ex-smokers, had lower PCS score, had less muscle strength and muscular exercise capacity, had lower FEV1, FVC and ejection fraction (EF) as measured by echocardiography. The low-capacity group more often used beta blockers and less mycophenolate, had higher NT-proBNP, hs-TnT, triglycerides and lower hemoglobin (Hgb). Duration of heart failure before HTx, primary diagnosis, donor age, ischemic time, rejection scores, MCS score and HADS depression score were similar between the two groups (Table 1).

Exercise variables

Exercise variables are shown in Table 2. As compared with the high-capacity group, the low-capacity group exercised for a shorter time, had lower maximal ventilation, O_2 pulse, HR_{peak} and $HR_{reserve}$, while VE/VCO_2 slope was higher (Table 2). The respiratory exchange ratio (RER), rated perceived exertion (RPE) and blood pressure responses were similar between the groups (Table 2).

Predictors of VO_{2peak}

Univariate predictors of VO_{2peak} are shown in Tables 1 and 2. There were strong correlations ($P < 0.001$) between VO_{2peak} and $HR_{reserve}$, O_2 pulse and muscular exercise capacity (Figures 1-3). In multiple regression analyses, O_2 pulse, $HR_{reserve}$, muscular exercise capacity, BMI, gender and age accounted for 84% of the variance in VO_{2peak} (L/min). Only O_2 pulse, $HR_{reserve}$ and muscular exercise capacity were important determinants in the final model ($P < 0.001$, $P < 0.001$ and $P < 0.015$, respectively). Other potential predictors were also analyzed in the multiple regression analyses, but these did not reach statistical significance. VO_{2peak} (L/min) was chosen as the dependent variable in order to be able to adjust for and see the impact of age, gender and BMI directly, as the VO_{2peak} (mL/kg per min) variable is already weight-based.

Safety

All measurements performed in this study, including the CPET and muscle strength testing, were completed without any minor or serious adverse events.

DISCUSSION

The main findings in this study were that *de novo* HTx patients display reduced exercise capacity compared with a general population: The reference population in ACSM[27] and Astrand[28], and that maximal exercise capacity was determined by both central (O_2 pulse and $HR_{reserve}$) and peripheral factors (muscular exercise capacity) (Table 3 and Figures 1-3). Furthermore, CPET can be safely performed as early as an average of 11 wk after HTx and is a valuable basis for individual tailoring of the further rehabilitation program.

Table 1 Clinical characteristics and health-related quality of life of the study population

[6]*N* = 55-81	Total	Low-capacity group (*n* = 41) VO_{2peak} ≤ 19.4 mL/kg per min	High-capacity group (*n* = 40) VO_{2peak} > 19.4 mL/kg per min	t (*P*-value)	Univariate regression Standardized coefficient Beta [95%CI], *P* VO_{2peak} (L/min)	[7]R^2
Clinical characteristics						
Sex (% men)	73%	66	80	0.152[1]	-0.45 [-0.61, -0.23], < 0.001	0.2
Age (yr)	49 ± 13	51 ± 11	46 ± 15	0.08	-0.19 [-0.01, -0.001], 0.093	0.04
Body mass index	25.3 ± 3.7	26.3 ± 3.4	24.2 ± 3.8	0.01	0.28 [0.007, 0.056], 0.013	0.08
Body fat (%)	25.1 ± 8.7	29.0 ± 8.3	21.0 ± 7.1	<0.001	-0.34 [-0.03, -0.006], 0.003	0.11
Donor age (yr)	34 (24, 49)	37 (27, 48)	33 (23, 52)	0.825[2]	0.09 [-0.004, 0.009], 0.447	0.01
Ischemic time (min)	210 (95, 237)	215 (99, 249)	185 (87, 227)	0.072[2]	-0.01[-0.001, 0.001], 0.938	8.2^{-5}
Weeks after HTx	11 ± 1.8	11.3 ± 2	10.9 ± 1.5	0.307	-0.001 [-0.05, 0.05], 0.990	2.0^{-5}
Duration of HF prior to HTx (yr)	4 (1.5, 10)	4 (1.5, 10.5)	4 (1.0, 9.3)	0.718[2]	-0.05 [-0.02, 0.01], 0.681	0.002
Time on HTx waiting list (d)	75 (24, 193)	96 (29, 227)	47 (12, 131)	0.06[2]	-0.14 [-0.001, 1.5-4], 0.202	0.02
Rejections grade 1-2 (% yes)	45	48	43	0.653[1]	0.09 [-0.11, 0.27], 0.408	0.01
VO_{2peak} preHTx (mL/kg per min)	11.6 ± 3.3	11.1 ± 3	12.1 ± 3.5	0.248	0.03 [-0.032, 0.039], 0.826	0.001
LVAD (% yes)	15	22	8	0.067[1]	-0.14 [-0.43, 0.097], 0.211	0.02
Preoperative IABP/ECMO (% yes)	16	15	18	0.725[1]	0.05 [-0.20, 0.32], 0.637	0.003
Postoperative IABP/ECMO (% yes)	10	15	5	0.264[3]	-0.26 [-0.68, -0.066], 0.018	0.07
Etiology HF (%)				0.138[3]		
Cardiomyopathy	65	56	75			
Ischemic heart disease	25	34	15			
Other	10	10	10			
Smoking (%) no/yes/ex-smoker	49/0/51	34/0/66	65/0/35	0.005[1]	-0.19 [-0.34, 0.03], 0.100	0.03
24 h ambulatory blood pressure						
Overall systolic BP	133 ± 12	133 ± 13	132 ± 10	0.672		
Overall diastolic BP	81 ± 7	80 ± 8	82 ± 7	0.493		
Medication (%)						
Ciclosporin	70	63	78	0.165[1]		
Tacrolimus	28	32	23	0.352[1]		
Everolimus	34	43	25	0.098[1]		
Mycophenolate	90	81	100	0.005[3]	0.29 [0.10, 0.71], 0.009	0.08
Prednisolone	100	100	100			
Beta-blocker	28	40	15	0.012[1]	-0.19 [-0.39, -0.03], 0.086	0.04
Calcium blocker	25	25	25	1.000[1]		
ACE inhibitors	3	3	3	1.000[3]		
AII-blocker	9	13	5	0.263[3]		
Diuretics	79	80	78	0.785[1]		
Statins	99	98	100	1.000[3]		
Blood samples						
TG (mmol/L)	1.7 (1.3, 2.5)	2.1 (1.5, 2.8)	1.5 (1.1, 2.2)	0.013[2]	-0.24 [-0,19, -0.002], 0.045	0.06
LDL (mmol/L)	2.9 ± 1.0	3.0 ± 1.2	2.9 ± 0.7	0.416	0.12 [-0.05, 0.15], 0.308	0.01
HDL (mmol/L)	1.5 ± 0.5	1.5 ± 0.5	1.6 ± 0.5	0.432	0.04 [-0.16, 0.22], 0.755	0.001
Cholesterol (mmol/L)	5.1 ± 1.3	5.3 ± 1.5	5.0 ± 1.0	0.329	0.03 [-0.07, 0.09], 0.830	0.001
Hemoglobin (g/dL)	11.8 ± 1.7	11.3 ± 1.9	12.2 ± 1.4	0.017	0.38 [0.042, 0.15], 0.001	0.14
hs-CRP (mg/L)	2.3 (1.0, 6.1)	2.7 (1.3, 6.7)	1.6 (0.6, 3.9)	0.052[2]	-0.17 [-0.015, 0.002], 0.125	0.03
NT-proBNP (ng/L)	968.3 (625.8, 1680.8)	1348.9 (765.4,2006.4)	790.7 (522.2, 1351.0)	0.005[2]	-0.36[-2.7E-4, -6.5^{-5}], 0.002	0.13
hs-TnT (ng/L)	32.5 (20.0, 61.8)	42.0 (27.8, 66.7)	24.0 (18.0, 50.8)	0.009[2]	-0.18 [-0.005, 0.001], 0.128	0.03
HbA1c (%)	5.6 ± 0.8	5.8 ± 0.9	5.4 ± 0.7	0.038	-0.15 [-0.19, 0.04], 0.213	0.02
Glucose (mmol/L)	5.9 ± 1.8	6.3 ± 2.1	5.5 ± 1.4	0.046	-0.19 [-0.1, 0.01], 0.109	0.04
Leukocytes ($\times 10^{-9}$/L)	5.4 ± 2.3	6.0 ± 2.7	4.7 ± 1.6	0.017	-0.06 [-0.05, 0.03], 0.580	0.004
Creatinine (μmol/L)	117.4 ± 31.4	118.0 ± 31.9	116.9 ± 31.3	0.868	-0.05 [-0.004, 0.002], 0.669	0.002
Carbamide (mmol/L)	9.8 ± 3.4	9.9 ± 4.0	9.7 ± 2.7	0.865	-0.003 [-0.03, 0.03], 0.977	1.00E-05
eGFR (mL/min per 1.73 m^2)	55 ± 16	54.1 ± 17.0	56.1 ± 15.0	0.586	0.23 [3.9E-5,0.01], 0.049	0.05
Muscle strength and muscular exercise capacity						
Muscle strength (Nm)	279 ± 129	231 ± 128	326 ± 113	0.001	0.66 [0.002, 0.003], < 0.001	0.43
Muscular Exercise capacity (J)	3229 ± 1660	2423 ± 1351	4015 ± 1567	< 0.001	0.64 [0.0001, 0.0002], < 0.001	0.41
Spirometry						
FEV1 (%)	81 ± 16	74 ± 14	88 ± 16	< 0.001	0.39 [0.004, 0.02], 0.001	0.16
PEF (%)	85 ± 22	79 ± 23	91 ± 20	0.018	0.37 [0.003, 0.01], 0.001	0.14
FVC (%)	86 ± 17	81 ± 16	90 ± 16	0.026	0.17 [-0.002, 0.01], 0.152	0.03
Echocardiography						
EF (%)	57.9 ± 5.6	56.2 ± 5.4	59.4 ± 5.4	0.011	0.26 [0.003, 0.04], 0.025	0.07
LVEDD (cm)	4.9 ± 0.5	4.9 ± 0.5	4.9 ± 0.4	0.996	0.42 [0.19, 0.59], < 0.001	0.18
FS (%)	36.7 ± 5.9	35.9 ± 6.8	37.5 ± 4.9	0.242	0.23 [-4.7E-5, 0.03], 0.051	0.05
CO (L/min)	6.1 ± 1.2	6.0 ± 1.2	6.2 ± 1.2	0.467	0.39 [0.06, 0.21], 0.001	0.15

Health-related quality of life						
PCS	43 ± 8	41 ± 7	45 ± 8	0.029	0.35 [0.008, 0.03], 0.001	0.13
MCS	54 ± 11	53 ± 10	55 ± 11	0.416	0.17 [-0.002, 0.02], 0.127	0.03
Symptoms of anxiety and depression						
HADS-A ⩾ 8 (%)[4]	15	17	13	0.562[1]	-0.26 [-0.56, -0.05], 0.02	0.07
HADS-D ⩾ 8 (%)[5]	5	5	5	1.000[3]	-0.16 [-0.73, 0.13], 0.165	0.03

Groups are divided according to the median VO_{2peak} (mL/kg per min). Variables are presented as percentages, mean ± SD or as median (Q1, Q3) where appropriate. [1]χ^2; [2]Mann Whitney U-test; [3]F; [4]HADS-A score ⩾ 8 indicates symptoms of anxiety; [5]HADS-D score ⩾ 8 indicates symptoms of depression; [6]The actual N varies from 55 to 81 for different variables; [7]Unadjusted R^2. ACE: Angiotensin-converting enzyme; ATII: Angiotensin Ⅱ; BP: Blood pressure; CO: Cardiac output; ECMO: Extracorporeal membrane oxygenation; EF: Ejection fraction; FEV_1: Forced expiratory volume at 1 min; FVC: Forced vital capacity; FS: Fractional shortening; HADS: Hospital anxiety and depression scale; HbA1c: Hemoglobin A1c; HDL: High density lipoprotein; hs-CR: High-sensitive C-reactive protein; hs-TnT: High-sensitive troponin T; HTx: Heart transplantation; IABP: Intra-aortic balloon pump; LVAD: Left ventricle assist device; LVEDD: Left ventricular end diastolic diameter; MCS: Mental component summary; Nm: Newton meter; NT-pro BNP: N-terminal pro brain natriuretic peptide; PEF: Peak expiratory flow; PCS: Physical component summary; Q1: First quartile; Q3: Third quartile; SD: Standard deviation; TG: Triglyceride.

Table 2 Cardiopulmonary responses to exercise of the study population

[2]*N* = 63-81	Total	Low-capacity group VO_{2peak} ⩽ 19.4 mL/kg per min (*n* = 41)	High-capacity group VO_{2peak} > 19.4 mL/kg per min (*n* = 40)	t (*P*-value)	Univariate regression Standardized coefficient Beta [95%CI], *P* VO_{2peak} L/min	[3]R^2
VO_{2peak} (mL/kg per min)	20.4 ± 4.9	16.4 ± 2	24.3 ± 3.6	< 0.001	0.75 [0.05, 0.08], < 0.001	0.56
VO_{2peak} (L/min)	1.6 ± 0.4	1.3 ± 0.3	1.8 ± 0.4	< 0.001		
%expected VO_{2peak}	55.8 ± 12.4	46.5 ± 7.4	65.3 ± 8.6	< 0.001	0.60 [0.01, 0.03], < 0.001	0.36
RER	1.2 ± 0.1	1.2 ± 0.14	1.2 ± 0.10	0.898		
HRrest (echocardiography)	87 ± 10	87 ± 11	86 ± 9	0.85	-0.07 [-0.013, 0.007], 0.551	0.01
Peak systolic BP (mmHg)	188 ± 30	188 ± 31	189 ± 30	0.865	0.19 [-0.001, 0.006], 0.108	0.04
Peak diastolic BP (mmHg)	82 ± 17	82 ± 18	82 ± 16	0.917	0.09 [-0.004, 0.008], 0.467	0.01
VE/VCO_{2slope}	34.8 ± 7.7	37.3 ± 7.2	32.6 ± 7.6	0.008	-0.42 [-0.035, -0.01], < 0.001	0.18
Vmax (L)	71.4 ± 22.8	60.5 ± 17.5	81.7 ± 22.7	< 0.001	0.76[0.01, 0.02], < 0.001	0.58
O_2 pulse (mL/beat)	12.4 ± 3.3	11.0 ± 3	13.7 ± 3	< 0.001	0.80 [0.08, 0.12], < 0.001	0.65
AT (L/min)	1.08 ± 0.3	0.95 ± 0.2	1.2 ± 0.3	0.001	0.73 [0.74, 1.2], < 0.001	0.53
METS	6.5 ± 1.6	5.4 ± 0.8	7.8 ± 1.3	< 0.001	0.77 [0.16, 0.24], < 0.001	0.59
HRpeak (beats/min)	128 ± 19	121 ± 19	134 ± 17	0.001	0.31 [0.002, 0.01], 0.005	0.1
%HRmax	75 ± 12	72 ± 12	78 ± 11	0.021	0.20 [-0.001, 0.02], 0.071	0.04
HRreserve (beats/min)	43 ± 16	35 ± 13	50 ± 15	< 0.001	0.47 [0.01, 0.02], < 0.001	0.22
CRI	0.51 ± 0.2	0.45 ± 0.18	0.57 ± 0.2	0.004	0.31 [0.20, 1.12], 0.005	0.1
RPE (Borg scale)	18.6 ± 0.8	18.5 ± 1	18.6 ± 0.5	0.638		
Test duration (min)	9.5 ± 2.8	7.8 ± 1.5	11.1 ± 2.7	< 0.001		
HRrecovery						
Beats /min at 2 min	-1.0 (-3.0, 1.0)	-1.0 (-3.0, 1.0)	-2.0 (-3.3, 1.3)	0.697[1]		

Groups are divided according to the median VO_{2peak} (mL/kg per min). Variables are presented as mean ± SD or as median (Q1, Q3) where appropriate. [1]Mann Whitney *U*-test; [2]The actual N varies from 63 to 81 for different variables; [3]Unadjusted R^2. BP: Blood pressure; CI, confidence interval; CRI, chronotropic response index; HR, heart rate; METS, metabolic equivalents; Vmax, maximum ventilation; Q1, first quartile; Q3, third quartile; RER, Respiratory Exchange Ratio; RPE, rated perceived exertion; SD, standard deviation.

Table 3 Multiple regression analysis

N = 66	Model 1 Standardized coefficient Beta [95% CI]	*P*-value	Model 2 Standardized coefficient Beta [95% CI]	*P*-value
O_2 pulse (mL/beat)	0.707 [0.075, 0.104]	< 0.001	0.675 [0.069, 0.102]	< 0.001
HRreserve (beats/min)	0.382 [0.007, 0.013]	< 0.001	0.397 [0.008, 0.013]	< 0.001
Muscular exercise capacity (Joule)	0.162 [1.1E-5, 7.1E-5]	0.008	0.155 [8.0^{-5}, 7.1^{-5}]	0.015
BMI (kg/m^2)			0.067 [-0.004, 0.020]	0.211
Sex			-0.029 [-0.142, 0.086]	0.630
Age (yr)			0.019 [-0.003, 0.004]	0.719
Adjusted R^2	0.85		0.84	

Dependent variable VO_{2peak} L/min. Final model for *n* = 66. BMI: Body mass index; CI: Confidence interval; HR: Heart rate.

In addition to the main predictors mentioned above, self-reported physical function was also positively associated with VO_{2peak} in this cohort, which is in accordance with an earlier paper from our research team[15]. Similar findings are reported from the general population in the Norwegian HUNT study, in which physical activity level

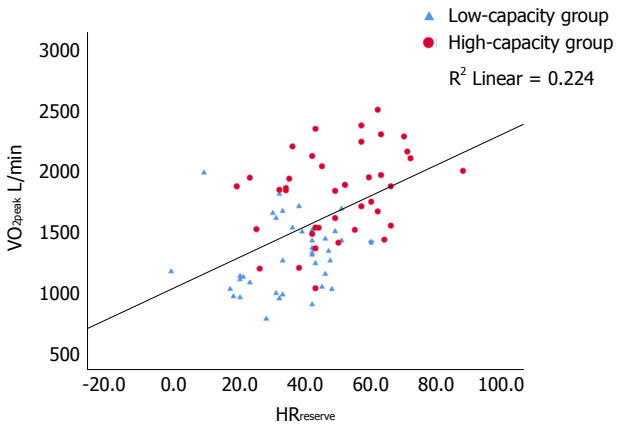

Figure 1 Scatterplot of the correlation between peak oxygen consumption (L/min) and heart rate reserve with inserted regression line. R^2 = 0.224. Pearsons *r* 0.473, *P* < 0.001. VO_{2peak}: Peak oxygen consumption; $HR_{reserve}$: Heart rate reserve.

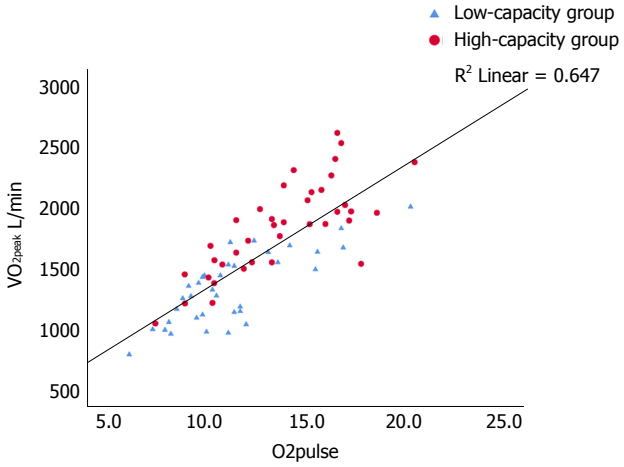

Figure 2 Scatterplot of the correlation between peak oxygen consumption (L/min) and O2 pulse with inserted regression line. R^2 = 0.647. Pearsons *r* 0.804, *P* < 0.001. VO_{2peak}: Peak oxygen consumption.

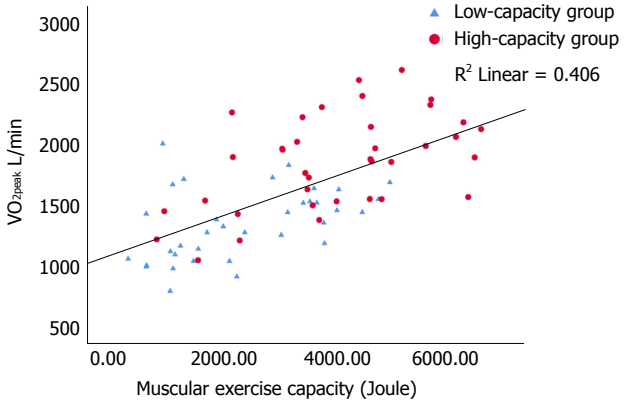

Figure 3 Scatterplot of the correlation between peak oxygen consumption (L/min) and muscular exercise capacity (Joule) with inserted regression line. R^2 = 0.406. Pearsons *r* 0.637, *P* < 0.001. VO_{2peak}: Peak oxygen consumption.

was associated with VO_{2peak}[29]. Although both groups in our current study had a lower score on the physical function subscale compared to the norm values described in Ware *et al*[25], the high-capacity group had a clinical meaningful and significantly higher score than the low-capacity group on physical function. The high-capacity group also had higher score on the PCS. On the other hand, there were no differences between the two groups regarding the psychosocial subscales or MCS in SF-36v2.

As previously mentioned, only two previous studies exist that describe determinants for VO_{2peak} in *de novo* HTx recipients[6,12]. Kitagaki *et al*[6] found that knee extensor muscle strength and cholinesterase were important predictors for VO_{2peak} 55 d after surgery. Salyer *et al*[12] found that age was the only predictor of $VO_{2\ peak}$ 68 d after HTx, but they did not include muscular exercise capacity or chronotropic variables in their regression analyses. A small study (*n* = 15) by Oliveira Carvalho *et al*[30] described that $HR_{reserve}$, as the only important variable, was associated with VO_{2peak} six months after HTx, while in maintenance HTx recipients, $HR_{reserve}$ was no longer strongly associated with VO_{2peak}. In $HR_{recovery}$ after exercise, there was an important difference between early and late HTx recipients, suggesting a partial reinnervation in maintenance HTx recipients[30]. However, peripheral factors such as muscular exercise capacity were not measured in Oliveira Carvalho's study[30]. Borelli *et al*[31] followed HTx recipients for two years and found that both central and peripheral factors contributed to the reduced VO_{2peak} both early (5.3 mo) and late (2 years) after HTx, but that the improvements in VO_{2peak} seen over two years were mostly related to peripheral factors.

In the present study, both $HR_{reserve}$ and O_2 pulse were independent predictors of VO_{2peak}. The chronotropic responses, CRI, $\%HR_{max}$ and HR_{peak} were, as expected, lower than normal both in the low-capacity and the high-capacity group. However, the high-capacity group had better chronotropic responses than the low-capacity group (CRI, *P* = 0.004; $\%HR_{max}$, *P* = 0.021, HR_{peak}, *P* = 0.001; $HR_{reserve}$, *P* < 0.001). $HR_{recovery}$ was markedly delayed in both groups, with no difference between the groups. Previous studies in maintenance HTx recipients have reported conflicting results whether chronotropic incompetence is associated with a reduced VO_{2peak} or not. Schwaiblmair *et al*[32] and Kemp *et al*[33] found a higher VO_{2peak} in patients with a greater $HR_{reserve}$, compared to patients with a lower $HR_{reserve}$. In contrast, Squires *et al*[34] found no difference in VO_{2peak} between patients with high versus low $HR_{reserve}$ (46 ± 15 *vs* 33 ± 15). In a previous study by our research group, where maintenance HTx recipients demonstrated a close to normal chronotropic response, $HR_{reserve}$ was not a strong determinant of VO_{2peak}[20]. However, in this current study of *de novo* HTx recipients, it is (Figure 1). The findings described above suggest that as the initially impaired chronotropic responses improve over time, they become less predictive of VO_{2peak}.

O_2 pulse derived from CPET is considered a surrogate for stroke volume[14,35,36]. In the current study, there was a strong correlation between $VO_{2\ peak}$ and O_2 pulse (Figure 2). In line with this, the high-capacity group also had a

higher O_2 pulse ($P < 0.001$), increased left ventricular EF, as well as lower NT-proBNP and hs-TnT levels, reflecting a better preserved myocardial function compared with the low-capacity group.

De novo HTx recipients have reduced muscle mass mostly due to inactivity prior to HTx[18]. The high-capacity group had higher muscular exercise capacity ($P < 0.001$) and muscular strength ($P = 0.001$) than the low-capacity group (Figure 3), and this finding supports the previously described association between muscle function and VO_{2peak}[20]. Comparing the muscle strength values from our previous study on maintenance recipients[20] with the values in this current study, they are not surprisingly much lower in the *de novo* recipients. As muscular exercise capacity is the only peripheral predictor for VO_{2peak} in the current study, peripheral factors might be less dominant than central factors in the early phase after HTx. However, from a clinical point of view, resistance training in the early rehabilitation after HTx is of high importance in order to prevent and restore loss of muscle mass and bone density and is likely to contribute to an improved VO_{2peak} level[37].

In the existing literature, VO_{2peak} in *de novo* HTx patients is reported to range from 9.2 mL/kg per min up to 19.7 mL/kg per min (1-3 mo after HTx)[2-12]. One small study of nine patients with left ventricle assist device (LVAD) prior to HTx had a mean VO_{2peak} of 24.6 mL/kg per min 12 wk after HTx, which is higher than what has been reported in other studies and may be explained by the LVAD effect and the patients' relatively high VO_{2peak} before HTx[38]. Except for this study, our cohort's mean VO_{2peak} level of 20.4 mL/kg per min (measured 11 wk post HTx) is higher than what is previously reported in *de novo* HTx recipients. Compared to an earlier exercise study in maintenance HTx recipients from our center with a median VO_{2peak} value of 27.3 mL/kg per min[20], this *de novo* HTx cohort is below this value, but compared to other international studies in maintenance HTx recipients, our current *de novo* HTx recipients are close to these reported values[18]. This may be partially related to the early and individualized exercise program conducted at our centers, where the patients are attended to daily by a physical therapist from the multidisciplinary HTx team.

Results from a CPET test can be important in many aspects in the early phase after HTx. First of all, a maximal exercise test is of great value to the individual patient in terms of contributing to increased confidence in their new heart and the body's tolerance to high-intensity exercise. Secondly, an early CPET is useful for deciding and tailoring the individual exercise programs and for the further rehabilitation, both for monitoring patients' status and prognosis and measuring effect of exercise. In addition to the many gas exchange variables, the CPET also provides other valuable and useful measurements, such as lung function and chronotropic responses. Finally, as we know that measures of physical capacity are strong predictors for long-term survival in HTx recipients[15,16], we suggest that such measures should be routinely included both in the early phase after HTx and at yearly controls thereafter. We underscore that the safety aspect is very important when performing a CPET and it should always be supervised by competent and experienced health personnel.

Limitations

Selection bias is a common risk in all voluntary studies, and although our aim was to include every newly transplanted HTx recipient, the recipients had to be medically stable and able to perform a maximal CPET and other physical tests. Thus, as the median VO_{2peak} value in this *de novo* cohort is comparable to maintenance HTx recipients' VO_{2peak} values, this may be due to a possible selection bias.

This is a cross-sectional study, based on the baseline data from an ongoing RCT, and no causal relationships should be drawn from such a study design. We present only associations between VO_{2peak} and different possible determinants. A rather small sample size ($n = 81$) may also imply type 2 errors, but all the performed statistics were carefully checked for underlying assumptions.

In this *de novo* HTx cohort, the age-predicted mean VO_{2peak} value was 56% of age-expected values, which is comparable to previously reported values in maintenance HTx[18]. Predictors for VO_{2peak} in *de novo* HTx recipients seem to be of both central (O_2 pulse and $HR_{reserve}$) and peripheral (muscular exercise capacity) origin. A CPET and determination of muscular exercise capacity provide important information for patient motivation, rehabilitation and prognosis and thus, measurements for physical function should be considered as routine examinations early after HTx.

ACKNOWLEDGMENTS

We especially thank the transplantation nurses Anne R Authen and Ingelin Grov for help and support throughout the study. From the University of Gothenburg, we thank the PhD student Andreas Lundberg Zachrisson and Professor Stefan Grau for help with the muscle strength testing among the Swedish participants. An abstract with data from this study was presented at the International Society for Heart and Lung Transplantation (ISHLT) 37th Annual Meeting and Scientific Sessions in San Diego 2017 and the ISHLT 38th Annual Meeting and Scientific Sessions in Nice 2018.

ARTICLE HIGHLIGHTS

Research background

Peak oxygen consumption (VO_{2peak}) is reduced after heart transplant (HTx). Both peripheral and central factors are determinants of the reduced VO_{2peak} in maintenance HTx recipients, but there are still few studies among *de novo* HTx patients. A higher VO_{2peak} is associated with better prognosis after HTx, and knowledge about predictors for VO_{2peak} in *de novo* HTx is important for the rehabilitation process. A cardiopulmonary exercise test (CPET) is the gold standard for measuring VO_{2peak} and should be performed as a routine test early after HTx.

Research motivation

More knowledge about predictors for VO_{2peak} in *de novo* HTx patients may contribute to a better understanding of the reduced exercise capacity early after

HTx. Individualized exercise prescriptions are very important after HTx, and a CPET early after HTx will guide both clinicians and physiotherapists in this vulnerable phase of the rehabilitation process.

Research objectives

The aim of this study was to investigate determinants of early VO_{2peak} and exercise capacity in a cohort of *de novo* HTx recipients.

Research methods

This study used baseline data from an ongoing randomized controlled trial investigating high-intensity interval training compared to moderate continuous exercise training among *de novo* HTx recipients, the HITTS study. A cross sectional analysis was performed on the baseline data from the 81 patients included in the study, and all baseline tests were performed an average of 11 wk after surgery. The primary endpoint was VO_{2peak} measured by CPET. Secondary endpoints were lung function, maximum muscle strength and muscular exercise capacity, bioelectrical impedance analysis, echocardiography, blood samples and health-related quality of life.

Research results

The main findings in this study were that *de novo* HTx patients display reduced exercise capacity compared to a general population, but comparable with maintenance HTx recipients. This *de novo* HTx cohort demonstrated a median VO_{2peak} level of 19.4 mL/kg per min at 11 ± 1.8 wk post-HTx. Maximal exercise capacity was determined by both central (O_2 pulse and $HR_{reserve}$) and peripheral factors (muscular exercise capacity). The CPET tests were performed without any serious adverse events mean 11 wk after HTx. This is a cross-sectional study, and no causal relationships should be drawn from such a study design. We present only associations between VO_{2peak} and different possible determinants.

Research conclusions

In this *de novo* HTx cohort, the age-predicted mean $VO_{2\ peak}$ value was 56% of age-expected values, which is comparable to previously reported values in maintenance HTx. Predictors for VO_{2peak} in *de novo* HTx recipients seem to be of both central and peripheral origin.

Research perspectives

A CPET and determination of muscular exercise capacity provide important information for patient motivation, rehabilitation and prognosis and thus, measurements for physical function should be considered as routine examinations early after HTx.

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P- Reviewer: Boteon YL, Gonzalez F, Hanna R, Hibberd AD
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